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Design, synthesis and acaricidal/insecticidal activities of etoxazole analogues

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Based on the structure–activity relationship of etoxazole analogues and benzoylphenylureas, a series of 2-(2,6-difluorophenyl)-4-(4-substitutedphenyl)-1,3-oxazolines **4a–y** were designed and synthesized. It was found that most of these compounds showed excellent acaricidal activities. They gave above 85% mortality at a concentration of 2.5 mg L^{-1}, both for the eggs and larvae of spider mites. Some compounds also showed excellent insecticidal activities. The position and type of the substituents on the 4-phenyl of 2,4-diphenyl-1,3-oxazoline have a great influence on the activities. 2-(2,6-Difluorophenyl)-4-(2-Cl-4-(4-Cl-phenoxy)phenyl)-1,3-oxazoline (**4r**) exhibited 100% acaricidal mortality at 2.5 mg L^{-1}, with 65% and 93% mortality against beet armyworm and diamondback moth, respectively, at 12.5 mg L^{-1}, which is almost the same level as etoxazole. The newly found structure–activity relationship may also benefit further acaricide/insecticide development.

Introduction

Etoxazole (**1**, Fig. 1), discovered by Kyoyu Agri Co., Ltd (formerly Yashima Chemical Industry Co., Ltd) and launched in 1998, is the only commercialized acaricide/insecticide belonging to the chemical class of 2,4-diphenyl-1,3-oxazolines.[1] Before and after its launch to the market, the three parts of its structure (**2**), especially parts A and C were extensively investigated by numerous companies. According to the structure–activity relationship studies (SARs), it is easy to find that the substituent effect of the 2-phenyl moiety (part A) of 2,4-diphenyl-1,3-oxazoline analogs (**2**) on the acaricidal activity against *T. urticae* is very similar to that of the benzoyl moiety (part A) of benzoylphenylureas (**3**) for the inhibition of chitin synthesis.[2,3] For both classes of structures, the compounds bearing a 2,6-difluorophenyl group give higher activities. There are also close similarities on the 4-phenyl moiety (part C) of **2** and phenyl moiety (part C) of **3**.[2] The quantitative structure–activity relationship studies (QSARs) on the 4-phenyl moiety of **2**[4,5] reveal that the presence of long chain *para* substituents containing an electronegative atom directly attached to the 4-phenyl ring may increase the ovicidal activity against *T. urticae*, and less lipophilic substituents at the *meta*-position of the 4-phenyl ring may be favorable for the activity. Similarly, for benzoylphenylureas (**3**), optimum hydrophobic and steric effects and the electron nature of substituents (Y) have been shown to be needed for substituents at this position. Halogens, CF_3 and alkyl (C4–C8) as well as substituted phenyl, benzyloxy and aryloxy substituents can be introduced into the *para*-position. Lower halogens, such as F and Cl, and CF_3 can occupy the *ortho*- and *meta*-positions to regulate or modify the effect of the entire phenyl moiety.[6,7]

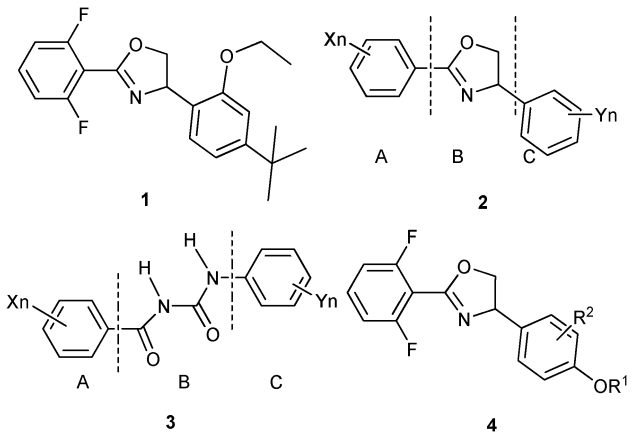

Fig. 1 Chemical structures of compounds **1–3** and designed target compound **4**.

In 2006, Nauen *et al.* found etoxazole can inhibit the incorporation of the radiolabelled chitin precursor [$^{[14]}$C]GluNAc into the integuments of pest invertebrates (EC_{50} is 2.95 μmol L^{-1}), therefore confirming the hypothesis that the acaricidal and insecticidal mode of action of etoxazole is chitin biosynthesis inhibition, which is similar to benzoylphenylureas (**3**), the

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well-known class of insecticidal chitin biosynthesis inhibitors.[8] Therefore, the optimization of the C part of 2,4-diphenyl-1,3-oxazoline (**2**), by mimicking the optimum of C part in benzoylphenylureas (**3**), seems more reasonable and evokes great interest.[9–11]

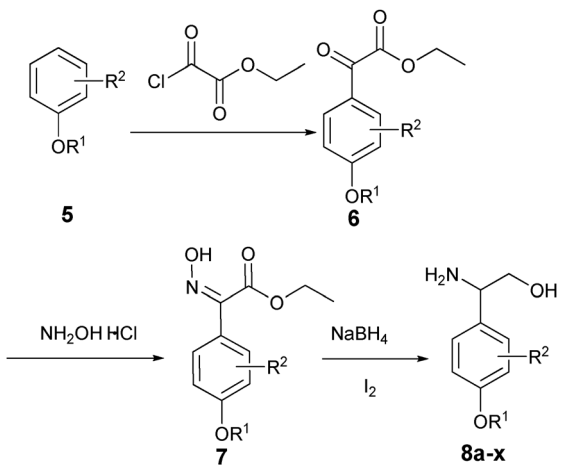
From the available QSAR results on **2**,[4,5] we found that compounds bearing an alkyl group at the *para*-position of the 4-phenyl ring of **2**, together with a proper *ortho*-position substituent, have been fully investigated, and etoxazole is one of the most successful examples. Upon combining the QSAR results of **2** and **3**,[9–11] it was supposed that the compounds with a phenoxy or alkoxy group at the *para* position of the 4-phenyl ring of **2**, together with a proper substituent at the *ortho*- or *meta*-position, would also afford high acaricidal activity, and the larvicidal activity against insect might also be extended; however, this part has not been fully investigated up till now.

On the basis of the above mentioned QSARs, we would like to report the synthesis and acaricidal/insecticidal activities of compounds **4a–y** (Fig. 1), in which 2,6-difluorophenyl was fixed at the 2-position of 1,3-oxazoline, and a substituted phenoxy or a different alkoxy group was fixed at the *para*-position of the 4-phenyl, optionally with Cl, methyl or ethoxy at the *ortho*-position and/or *meta*-position. The structure–activity relationships between the substituents on 4-phenyl and the acaricidal/insecticidal activities are mainly discussed to provide fundamental support for the development of novel structured acaricidal/insecticidal agents.

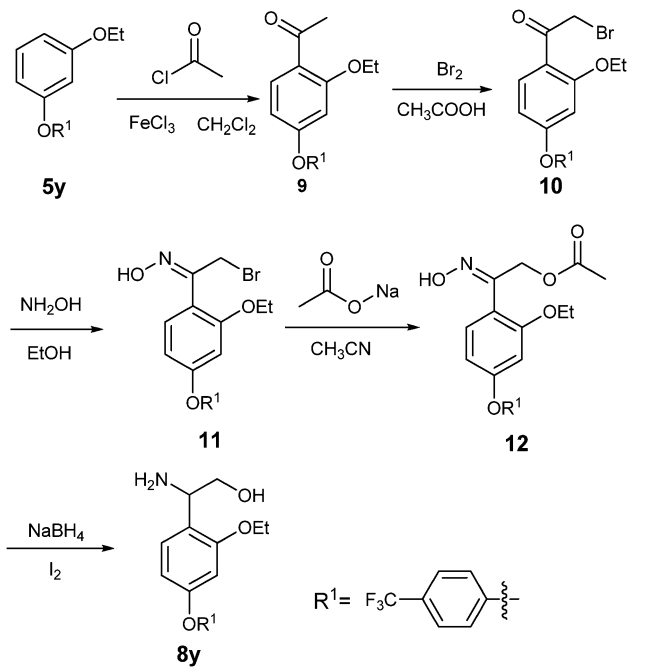
Results and discussion

Synthesis

Intermediate aminoalcohols (**8a–x**) were prepared according to the literature[2] with some modification (Scheme 1). α-Ketoester **6** was prepared by a Friedel–Crafts-type reaction of substituted benzene **5** with ethyl chloroglyoxylate. **6** was converted to hydroxyiminoester **7** by condensation with hydroxylamine, and then **7** was reduced by sodium borohydride to give aminoalcohol **8**. When the R^1 was 4-CF_3-phenoxy, the Friedel–Crafts reaction of **5y** with ethyl chloroglyoxylate was found to be complicated; therefore aminoalcohol **8y** was prepared using a different method which is illustrated in Scheme 2. Benzene **5y** was acetylated first in the presence of $FeCl_3$, and then the resulting methyl ketone **9** was successively reacted with bromine, hydroxylamine hydrochloride and sodium acetate to form **12**, **12** was finally reduced by sodium borohydride to give aminoalcohol **8y**.



Scheme 1 Synthesis of intermediate **8a–x**.

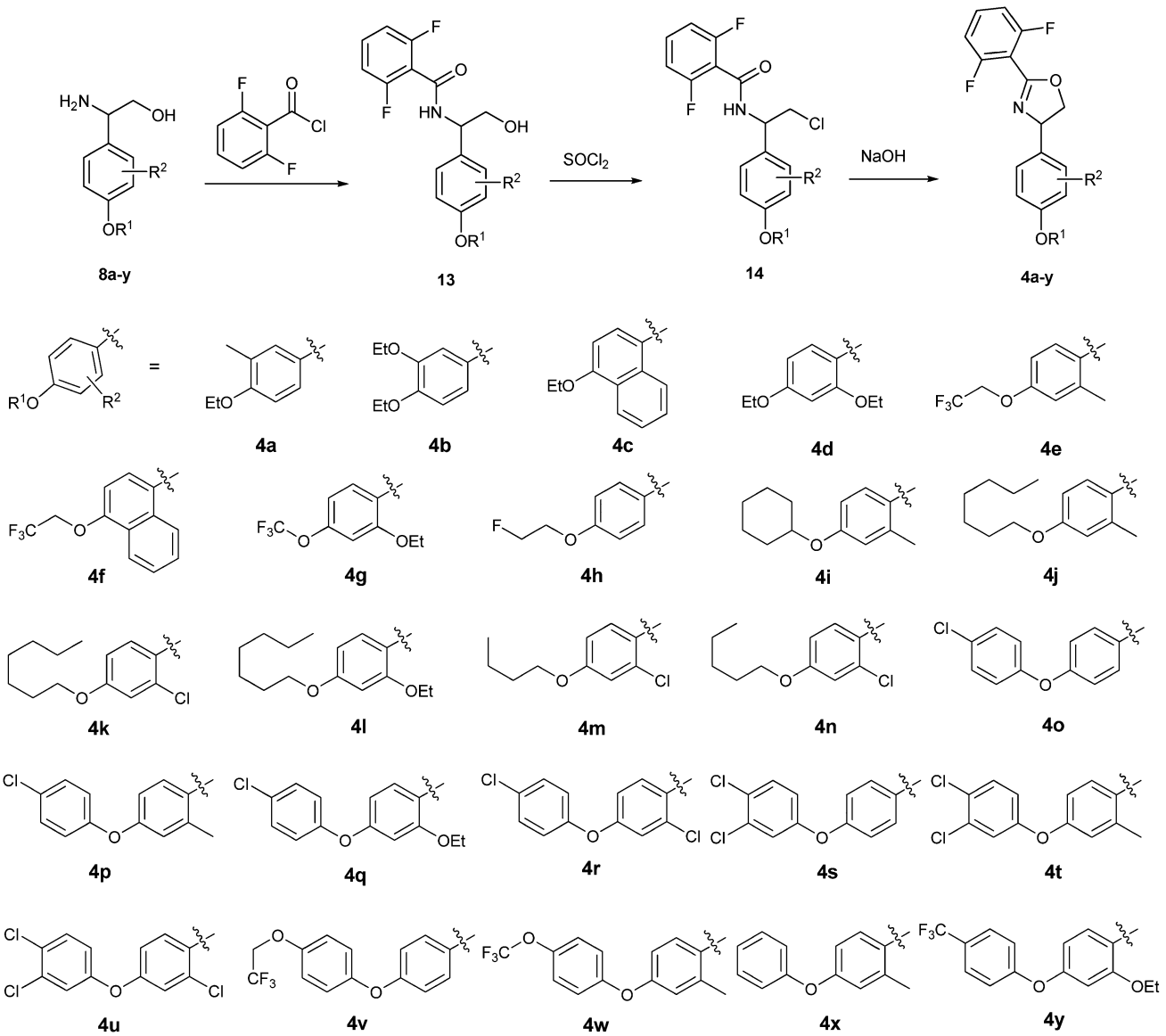


Scheme 2 Synthesis of intermediate **8y**.

The general synthetic route of 2-(2,6-difluorophenyl)-4-(4-substitutedphenoxyphenyl)-1,3-oxazolines **4a–y** are shown in Scheme 3. Aminoalcohol **8** first reacted with 2,6-difluorobenzoyl chloride to give amidoalcohol **13**, and then **13** was treated with thionyl chloride to convert the hydroxy group to chloride. In the presence of sodium hydroxide, the amido group in **14** tautomerized to hydroxyimine and the oxygen nucleophilically attacked the chlorine-attached carbon atom, resulting in the cyclization to 2-(2,6-difluorophenyl)-4-(4-substitutedphenoxyphenyl)-1,3-oxazolines **4**.

Bioactivity and the structure–activity relationship

The acaricidal activities of the synthesized 2,4-diphenyl-1,3-oxazolines **4a–y** and control compound etoxazole against eggs and larvae of spider mites by the leaf-dip method are listed in Table 1. As expected, most of the 4-alkoxysubstituted or 4-(phenoxysubstituted)phenyl-1,3-dioxazoline compounds showed excellent acaricidal activities at a concentration of 2.5 mg L^{-1}; they gave a 95–100% mortality rate for eggs and above 85% mortality for larvae. From the three compounds bearing a 4-ethoxy group at the 4-phenyl (compounds **4a**, **4b** and **4d**), it was found that the position and types of additional substituents at the 4-phenyl tuned the activity. For example, the (4-ethoxy-3-methyl)phenyl compound **4a** gave a much higher activity than that of the (4-ethoxy-3-methoxy)phenyl compound **4b**; and **4b** had a much lower activity than the (2,4-diethoxy)phenyl compound **4d**.



Scheme 3 Synthesis of target compounds **4a–y**.

4-Ethoxynaphthyl compound **4c** (could also be regarded as 2,3-disubstituted-4-ethoxyphenyl compound) gave the least activity, which also confirmed that the substituents on the phenyl ring had a significant effect on the activity. 4-(4-Heptoxyphenyl) compounds **4j** (with a 2-methyl group at the phenyl, and 86% mortality on larvae at 2.5 mg L^{-1}), **4k** (with a 2-chloro group and 95% mortality) and **4l** (with a 2-ethoxy group and 90% mortality) also gave different larvicidal activities. However, for the 4-(4-chlorophenoxy)-phenyl compounds (**4o–4r**) and 4-(3,4-dichlorophenoxy)phenyl (**4s–4u**), the differences were not so distinct; most of them exhibited 100% mortality at 2.5 mg L^{-1}. Compared to the 4-ethoxynaphthyl compound **4c**, the 4-trifluoroethoxynaphthyl compound **4e** exhibited much better activity against both eggs and larvae, this indicated that the substituent on the 4-position was also significant. This can also be confirmed from the different activities of the 2-ethoxyphenyl compounds **4d** (94% mortality against larvae at a concentration of 2.5 mg L^{-1}), **4g** (87%), **4l** (90%), **4q** (100%) and **4y** (100%), which had a 4-ethoxy, 4-trifluoromethoxy, 4-heptoxy, 4-(4-chlorophenoxy) and 4-(4-trifluoromethylphenoxy) at the 2-ethoxyphenyl respectively. Similarly, compounds with a 2-methylphenyl group (**4e**, **4i**, **4j**, **4p**, **4t**, and **4w**) confirmed the same deduction, and also suggest a (substituted) phenoxy group was more suitable than an alkoxy at the *para*-position. From the above discussion, we conclude that the substituents at the *para*- and *ortho*-positions of the 4-phenyl of 1,3-dioxazole have a synergistic effect on the acaricidal activity, of which the *para* substituents play a more important role.

The insecticidal activities of **4a–y**, and the control compound etoxazole, against diamond-back moths as determined by the leaf-dip method are listed in Table 2. The structure–activity relationship is a little different from that for acaricidal activity. It was found that the 2- or 3-substituent played the dominant

Table 1 Acaricidal activities against spider mites (mortality rates, %)

	Activities (%) against eggs at concentration (mg L^{-1})				Activities (%) against larvae at concentration (mg L^{-1})			
Compd	100	50	25	2.5	100	50	25	2.5
4a	100	100	100	97	100	100	96	94
4b	100	89	0	—	100	91	0	—
4c	86	0	—	—	89	0	—	—
4d	100	100	100	100	100	100	100	94
4e	100	100	100	100	100	100	100	92
4f	100	100	100	100	100	100	94	91
4g	100	100	100	100	100	100	91	87
4h	100	100	100	98	100	100	100	95
4i	100	100	100	100	100	98	92	88
4j	100	100	100	98	100	100	100	86
4k	100	100	100	100	100	100	100	95
4l	100	100	100	95	100	100	100	90
4m	100	100	100	98	100	100	100	100
4n	100	100	98	90	100	100	90	85
4o	100	100	100	100	100	100	100	100
4p	100	100	100	100	100	100	100	100
4q	100	100	100	100	100	100	100	100
4r	100	100	100	100	100	100	100	93
4s	100	100	100	100	100	100	100	100
4t	100	100	100	100	100	100	100	100
4u	100	100	100	100	100	100	100	100
4v	100	100	100	100	100	100	100	100
4w	100	100	100	100	100	100	97	96
4x	100	100	100	100	100	100	100	100
4y	100	100	100	100	100	100	100	100
Etoxazole	100	100	100	100	100	100	100	96

Table 2 Insecticidal activities against diamond-back moths (mortality rates, %)

Compd	200 mg L^{-1}	100 mg L^{-1}	50 mg L^{-1}	25 mg L^{-1}	12.5 mg L^{-1}
4a	100	100	63	41	0
4b	0	—	—	—	—
4c	0	—	—	—	—
4d	0	—	—	—	—
4e	86	75	53	0	—
4f	100	100	95	89	0
4g	100	100	100	95	72
4h	0	—	—	—	—
4i	0	—	—	—	—
4j	100	100	100	88	77
4k	100	100	100	100	87
4l	0	—	—	—	—
4m	100	90	86	71	43
4n	100	71	71	57	43
4o	100	100	61	0	—
4p	0	—	—	—	—
4q	0	—	—	—	—
4r	100	100	100	79	65
4s	0	—	—	—	—
4t	0	—	—	—	—
4u	100	71	43	0	0
4v	0	—	—	—	—
4w	0	—	—	—	—
4x	0	—	—	—	—
4y	65	0	—	—	—
Etoxazole	100	100	100	81	74

role. From the three compounds bearing a 4-ethoxy group at the 4-phenyl (compounds **4a**, **4b** and **4d**), compound **4a**, with a 3-methyl on the 4-ethoxyphenyl group, had a higher mortality than other two compounds. Among the compounds bearing 4-*n*-heptoxy (**4j–l**), 4-(4-chlorophenyl) (**4o–r**) or 4-(3,4-dichlorophenyl)phenyl

Table 3 Insecticidal activities against beet armyworms (mortality rates, %)

Compd	200 mg L^{-1}	100 mg L^{-1}	50 mg L^{-1}	25 mg L^{-1}	12.5 mg L^{-1}
4a	100	100	71	0	0
4m	29	0	—	—	—
4n	14	0	—	—	—
4r	100	100	100	96	93
4u	29	14	0	0	0
Etoxazole	100	100	100	87	78

compounds (**4s–u**), always the compounds bearing a chlorine atom at the 2-position of the 4-phenyl (**4k**, **4r** and **4u**) gave higher mortality. Compounds **4m** and **4n**, also with a chlorine atom at the 2-position of 4-phenyl, gave high activity due to the same reason. Comparably, compounds with an ethoxy (**4d**, **4l**, **4q**, and **4y**) or a methyl (**4p**, **4t**, **4w** and **4x**) group at the 2-position of 4-phenyl always gave lower activities. It is noteworthy that compounds **4e–g** exhibited much better activity than the other 2-methyl or 2-ethoxy analogues; this may be explained as a result of the trifluoroethoxy or trifluoromethyl group at the 4-position of phenyl helping to increase the activity.

Compounds **4a**, **4m**, **4n**, **4r** and **4u** were also tested for their larvicidal activities against beet armyworms and the data are listed in Table 3. Compared with the activities against diamond-back moths in Table 2, the trends of activities against beet armyworms was not the same as in Table 2. Compounds **4a** and **4u**, which had lower activities against diamond-back moths than **4m** and **4n**, exhibited much higher activities against beet armyworms; therefore it suggested the compounds had some selectivity on the insecticidal spectrum. Of the compounds, 4-(4-chlorophenyl) compound **4r** stood out as having the best larvicidal activity, with a 93% mortality rate at 12.5 mg L^{-1} against beet armyworms, which is slightly higher than commercial etoxazole (78% mortality).

Conclusions

In summary, a series of 2,4-diphenyl-1,3-oxazolines containing 4-alkoxy or 4-(substituted)phenoxy groups at the 4-phenyl of 1,3-oxazolines were designed and synthesized. Their acaricidal activities against eggs and larvae of spider mites, and their insecticidal activities against diamondback moths and beet armyworms were evaluated. The results indicated that the positions and types of substituents on the 4-phenyl influenced the acaricidal and insecticidal activity, but with different structure–activity relationships. For acaricidal activity, the substituent on the *para* group at the 4-phenyl ring played a dominant role, while for insecticidal activity, the *ortho* group affected the activity greatly. Of all the compounds, 4-(2-chloro-4-(4-chlorophenoxy)phenyl)-2-(2,6-difluorophenyl)-1,3-oxazoline (**4r**) exhibited excellent acaricidal activities against the eggs and larvae of spider mites and larvicidal activities against both diamond back moths and beet armyworms, which were comparable with that of the commercial etoxazole. The newly found structure–activity relationship may be helpful for further designing and developing new 2,4-diphenyl-1,3-oxazolines as acaricidal/insecticidal agents. These designed compounds exhibited excellent acaricidal activity, which also indicated that

our design ideology is reasonable. As part of our ongoing progress, further studies on the acaricidal activity corresponding lower concentration, LC_{50} values, mode of action, and toxicity are currently underway in our laboratories and will be systematically described as an independent work.

Materials and methods

Instruments

All reactions were carried out under a nitrogen atmosphere with the exclusion of moisture. Proton NMR spectra were obtained at 300 MHz or 400 MHz using a Bruker AV300 or AV400 spectrometer. Chemical shift values (δ) are given in ppm and are downfield from internal standard tetramethylsilane. Elemental analyses were determined on an MT-3 elemental analyzer. High-resolution mass spectrometry (HRMS) data were obtained on a FTICR-MS instrument (Ionspec 7.0 T). The starting material **5** was either commercially available or prepared *via* etherification from the corresponding phenol.

General synthetic procedure for ethyl 2-(substituted)phenyl-2-oxoacetate (6)

A mixture of anhydrous $AlCl_3$ (0.74 g, 5.60 mmol) and ethyl chloroglyoxylate (0.76 g, 5.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature until $AlCl_3$ was dissolved. Then, substituted benzene **5** (4.66 mmol) in CH_2Cl_2 (30 mL) was added dropwise at 5 °C, and the reaction mixture was allowed to warm to the room temperature with stirring. After 2 h, the reaction mixture was poured into a mixture of concentrated HCl and ice. The organic layer was separated, and the aqueous layer was extracted twice with 60 mL of CH_2Cl_2. The combined organic layers were washed twice with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product **6**, which was used in the next reaction without further purification.

General synthetic procedure for ethyl 2-substitutedphenyl-2-hydroxyiminoacetate (7)

A mixture of the above 2-phenyl-2-oxoacetate **6** (2.5 mmol) and hydroxylamine hydrochloride (0.26 g, 3.75 mmol) in EtOH (100 mL) was refluxed with stirring for 5 h. The reaction mixture was then concentrated under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed twice with water and once with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product **7**, which was used in the next reaction without further purification.

General synthetic procedure for amino alcohols (8a–y)

To a solution of crude **7** or **12** (2.5 mmol) in THF (50 mL) was added $NaBH_4$ (0.29 g, 7.50 mmol), and then a solution of iodine (5 mmol) in THF (50 mL) was added dropwise over 2.5 h at 0 °C. The reaction mixture was then refluxed with stirring for 5 h, and then allowed to cool to room temperature. Methanol was added to the reaction mixture until it became clear. After the solvent was removed, to the residue was added 5% aqueous solution of NaOH (50 mL), which then refluxed for 3 h and was cooled to room temperature. The solution was extracted four times with 20 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products **8a–y**, which were used in the next reaction without further purification.

Synthetic procedure for 1-(2-ethoxy-4-(4-(trifluoromethyl)phenoxy)-phenyl)ethanone (9)

To a mixture of anhydrous $FeCl_3$ (1.20 g, 7.40 mmol) and acetyl chloride (0.56 g, 7.34 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of 1-ethoxy-3-(4-(trifluoromethyl)phenoxy)-benzene (**5y**) (2.00 g, 7.34 mmol) in CH_2Cl_2 (10 mL) at 5 °C. The reaction mixture was allowed to warm to room temperature with stirring for 12 h, and then was poured into ice water (50 mL). The organic layer was separated, and the aqueous layer was extracted twice with 20 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to give product **9** as a yellow thick oil (1.02 g, 44.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 2.61 (s, 3H), 3.96 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 6.42 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 6.70 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.4 Hz, 1H), 6.96 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.01 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 7.42 (d, $^3J_{HH}$ = 8.6 Hz, 2H).

Synthetic procedure for 2-bromo-1-(2-ethoxy-4-(4-(trifluoromethyl)-phenoxy)phenyl)-ethanone (10)

To a mixture of **9** (1.02 g, 3.15 mmol), acetic acid (10 mL) and hydrobromic acid (48%, 1 mL) was added bromine (0.5 g, 3.15 mmol) at 5 °C. The reaction mixture was allowed to warm to room temperature with stirring for 1 h, and then was poured into ice water (100 mL). The mixture was extracted twice with 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product **10**, which was used in the next reaction without further purification.

Synthetic procedure for bromomethyl oxime (11)

To crude **10** in ethanol (20 mL) was added hydroxylamine hydrochloride (0.26 g, 3.75 mmol) and water (20 mL), then the mixture was stirred at room temperature for 24 h. To the reaction mixture was added water (100 mL), followed by extraction with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product **11** as a yellow oil (0.92 g, 73%), which was used in the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 3.96 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 4.43 (s, 2H), 6.41 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 6.71 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.4 Hz, 1H), 6.96 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.02 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 7.42 (d, $^3J_{HH}$ = 8.6 Hz, 2H).

Synthetic procedure for acetate (12)

To a mixture of sodium acetate (1.72 g, 2.2 mmol) in water (30 mL) and acetonitrile (5 mL) was slowly added compound **11**

(0.92 g, 2.2 mmol) in acetonitrile (10 mL). After stirring at room temperature for 1 h, the mixture was poured into water (50 mL), and then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give **12** as a white solid (0.72 g, 83%). Mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 2.05 (s, 3H), 3.96 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 4.94 (s, 2H), 6.41 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 6.72 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.4 Hz, 1H,), 6.95 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.02 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 7.41 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.81 (s, 1H).

General synthetic procedure for amide (13)

To a stirred mixture of amino alcohol **8** (2.17 mmol) and triethylamine (0.24 g, 2.39 mmol) in THF (40 mL) was added dropwise a solution of 2,6-difluorobenzoyl chloride (0.42 g, 2.39 mmol) in THF (20 mL) at 5 °C. After stirring the reaction mixture at room temperature for 2 h, the precipitate was removed by filtration, and the solution was concentrated under reduced pressure to give crude compound **13**, which was used in the next reaction without further purification.

General synthetic procedure for 14

To a mixture of crude **13** in toluene (50 mL), thionyl chloride (0.75 g, 6.30 mmol) was added dropwise with stirring, and then the mixture was heated to 80 °C for 3 h. After cooling, to the reaction mixture was added a solution of Na_2CO_3 to make the pH = 8, then the organic layer was separated and concentrated under reduced pressure to give crude **14**.

General synthetic procedure for target compound 4

Compound **14** was dissolved in MeOH (50 mL) and treated with NaOH (0.15 g, 3.80 mmol). After stirring for 1 h at 50 °C, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford product **4**.

Data for **4a**: yield, 80%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 2.23 (s, 3H), 4.02 (q, $^3J_{HH}$ = 7.0 Hz, 2H), 4.25–4.31 (m, 1H), 4.74–4.81 (m, 1H), 5.35–5.41 (m, 1H), 6.79 (d, $^3J_{HH}$ = 8.7 Hz, 1H), 6.99 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.08–7.12 (m, 2H), 7.36–7.46 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{18}F_2NO_2$ (M + H)$^+$: 318.1300, found: 318.1296.

Data for **4b**: yield, 71%; white solid; Mp 71–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41–1.47 (m, 6H), 4.05–4.15 (m, 4H), 4.26–4.32 (m, 1H), 4.75–4.81 (m, 1H), 5.36–5.42 (m, 1H), 6.82–6.89 (m, 3H), 7.00 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.37–7.47 (m, 1H); anal. Calcd for $C_{19}H_{19}F_2NO_3$: C, 65.70; H, 5.51; N, 4.03; found: C, 65.83; H, 5.65; N, 4.01.

Data for **4c**: yield, 76%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 4.19–4.24 (m, 3H), 5.03–5.08 (m, 1H), 6.08–6.13 (m, 1H), 6.82 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.03 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.42–7.47 (m, 1H), 7.52–7.60 (m, 3H), 7.77 (d, $^3J_{HH}$ = 8.2 Hz, 1H,), 8.40 (d, $^3J_{HH}$ = 8.2 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{17}F_2NO_2Na$ (M + Na)$^+$: 376.1120, found: 376.1126.

Data for **4d**: yield, 50%; white solid; Mp 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, $^3J_{HH}$ = 6.9 Hz, 6H), 3.98–4.06 (m, 4H), 4.13–4.18 (m, 1H), 4.81–4.87 (m, 1H), 5.59–5.66 (m, 1H), 6.42–6.49 (m, 2H), 6.99 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.30 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.36–7.46 (m, 1H); anal. Calcd for $C_{19}H_{19}F_2NO_3$: C, 65.70; H, 5.51; N, 4.03; found: C, 65.45; H, 5.44; N, 3.98.

Data for **4e**: yield, 90%; white solid, Mp 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 4.11–4.15 (m, 2H), 4.39 (q, $^3J_{HH}$ = 8.0 Hz, 2H), 4.86–4.91 (m, 1H), 5.66–5.71 (m, 1H), 6.65 (s, 1H), 6.89 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 6.99 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.37 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.39–7.44 (m, 2H); anal. Calcd for $C_{18}H_{14}F_5NO_2$: C, 58.23; H, 3.80; N, 3.77; found: C, 58.19; H, 3.99; N, 3.92.

Data for **4f**: yield, 89%; white solid; Mp 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18–4.23 (m, 1H), 4.49–4.58 (q, $^3J_{HH}$ = 8.0 Hz, 2H), 5.03–5.09 (m, 1H), 6.08–6.15 (m, 1H), 6.82 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.04 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.41–7.49 (m, 1H), 7.55–7.60 (m, 3H), 7.81 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 8.37 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1H); anal. Calcd for $C_{21}H_{14}F_5NO_2$: C, 61.92; H, 3.46; N, 3.44; found: C, 61.60; H, 3.68; N, 3.33.

Data for **4g**: yield, 82%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 4.04 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 4.11–4.17 (m, 1H), 4.81–4.89 (m, 1H), 5.63–5.72 (m, 1H), 6.81 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 6.86 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 7.01 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.40 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.42–7.46 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}F_5NO_3$ (M + H)$^+$: 388.0967, found: 388.0967.

Data for **4h**: yield, 75%; white solid; Mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (t, $^3J_{HH}$ = 4.2 Hz, 1H), 4.23–4.29 (m, 2H), 4.69 (t, $^3J_{HH}$ = 4.2 Hz, 1H), 4.76–4.82 (m, 2H), 5.39–5.45 (m, 1H), 6.93 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.00 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.27 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.38–7.46 (m, 1H); anal. Calcd for $C_{17}H_{14}F_3NO_2$: C, 63.55; H, 4.39; N, 4.36; found: C, 63.57; H, 4.24; N, 4.53.

Data for **4i**: yield, 82%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.49 (m, 6H), 1.77–1.82 (m, 2H), 1.95–1.99 (m, 2H), 2.31 (s, 3H), 4.13–4.18 (m, 1H), 4.19–4.23 (m, 1H), 4.80–4.85 (m, 1H), 5.57–5.62 (m, 1H), 6.73 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 6.75 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 7.00 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.26 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.39–7.46 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}F_2NO_2$ (M + H)$^+$: 372.1770, found: 372.1766.

Data for **4j**: yield, 63%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 1.30–1.47 (m, 8H), 1.73–1.81 (m, 2H), 2.32 (s, 3H), 3.93 (t, $^3J_{HH}$ = 6.6 Hz, 2H), 4.11–4.17 (m, 1H), 4.80–4.86 (m, 1H), 5.57–5.63 (m, 1H), 6.74–6.78 (m, 2H), 7.00 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.28 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.38–7.46 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{27}F_2NO_2Na$ (M + Na)$^+$: 410.1902, found: 410.1902.

Data for **4k**: yield, 81%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 1.30–1.47 (m, 8H), 1.73–1.80 (m, 2H), 3.93 (t, $^3J_{HH}$ = 6.6 Hz, 2H), 4.12–4.17 (m, 1H), 4.90–4.95 (m, 1H), 5.71–5.76 (m, 1H), 6.82 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 6.94 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 7.01 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.38 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.41–7.47 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}ClF_2NO_2Na$ (M + Na)$^+$: 430.1356, found: 430.1357.

Data for **4l**: yield, 87%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 1.31–1.45 (m, 8H), 1.74–1.82 (m, 2H), 3.95

(q, $^3J_{HH}$ = 6.6 Hz, 2H), 4.05 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 4.16–4.20 (m, 1H), 4.83–4.88 (m, 1H), 5.61–5.66 (m, 1H), 6.45–6.49 (m, 2H), 7.01 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.30 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.38–7.46 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{24}H_{29}F_2NO_3Na$ $(M + Na)^+$: 440.2008, found: 440.2012.

Data for **4m**: yield, 58%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.44–1.53 (m, 2H), 1.73–1.79 (m, 2H), 3.95 (t, $^3J_{HH}$ = 6.5 Hz, 2H), 4.12–4.17 (m, 1H), 4.90–4.95 (m, 1H), 5.71–5.76 (m, 1H), 6.83 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.5 Hz, 1H,), 6.94 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 7.01 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.38 (d, $^3J_{HH}$ = 8.6 Hz 1H), 7.41–7.46 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{19}H_{19}ClF_2NO_2$ $(M + H)^+$: 366.1067, found: 366.1072.

Data for **4n**: yield, 69%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 1.35–1.45 (m, 4H), 1.74–1.82 (m, 2H), 3.94 (t, $^3J_{HH}$ = 6.5 Hz, 2H), 4.12–4.17 (m, 1H), 4.90–4.95 (m, 1H), 5.71–5.76 (m, 1H), 6.83 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 6.95 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 7.01 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.38 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.41–7.46 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{20}H_{21}ClF_2NO_2$ $(M + H)^+$: 380.1223, found: 380.1221.

Data for **4o**: yield, 87%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27–4.32 (m, 1H), 4.79–4.84 (m, 1H), 5.43–5.48 (m, 1H), 6.92 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 6.98–7.02 (m, 4H), 7.26–7.33 (m, 4H), 7.40–7.49 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClF_2NO_2$ $(M + H)^+$: 386.0754, found: 386.0759.

Data for **4p**: yield, 84%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.14–4.20 (m, 1H), 4.83–4.90 (m, 1H), 5.57–5.66 (m, 1H), 6.84–6.88 (m, 2H), 6.92 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.00 (t, $^3J_{HH}$ = 8.2 Hz, 2H), 7.27 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.36 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.41–7.46 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{22}H_{16}ClF_2NO_2Na$ $(M + Na)^+$: 422.0730, found: 422.0732.

Data for **4q**: yield, 83%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 3.94 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 4.17–4.23 (m, 1H), 4.72–4.79 (m, 1H), 5.59–5.66 (m, 1H), 6.41 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 6.71 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 6.92–7.01 (m, 4H), 7.28 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.39–7.42 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{23}H_{18}ClF_2NO_3Na$ $(M + Na)^+$: 452.0835, found, 452.0830.

Data for **4r**: yield, 72%; white solid; Mp: 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16–4.21 (m, 1H), 4.94–4.99 (m, 1H), 5.75–5.60 (m, 1H), 6.93–7.05 (m, 6H), 7.33 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.43–7.49 (m, 2H); anal. Calcd for $C_{21}H_{13}Cl_2F_2NO_2$: C, 60.02; H, 3.12; N, 3.33; found: C, 60.10; H, 3.23; N, 3.36.

Data for **4s**: yield, 89%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28–4.33 (m, 1H), 4.80–4.85 (m, 1H), 5.44–5.49 (m, 1H), 6.84 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.8 Hz, 1H), 6.98–7.03 (m, 4H), 7.06 (d, $^4J_{HH}$ = 2.8 Hz, 1H), 7.34–7.38 (m, 3H), 7.41–7.47 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{21}H_{13}Cl_2F_2NO_2$ $(M + H)^+$: 420.0364, found, 420.0366.

Data for **4t**: yield, 83%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.15–4.21 (m, 1H), 4.85–4.91 (m, 1H), 5.61–5.68 (m, 1H), 6.81–6.91 (m, 3H), 6.95–7.07 (m, 4H), 7.34–7.44 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{22}H_{15}Cl_2F_2NO_2$ $(M + H)^+$: 434.0521, Found, 434.0515.

Data for **4u**: yield, 90%; white solid; Mp: 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16–4.22 (m, 1H), 4.94–5.01 (m, 1H), 5.74–5.81 (m, 1H), 6.87 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.8 Hz, 1H), 6.95 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.4 Hz, 1H), 7.02 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.06 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 7.11 (d, $^4J_{HH}$ = 2.8 Hz, 1H), 7.39–7.52 (m, 3H); anal. Calcd for $C_{21}H_{12}Cl_3F_2NO_2$: C, 55.47; H, 2.66; N, 3.08; found: C, 55.69; H, 2.85; N, 3.31.

Data for **4v**: yield, 71%; white solid; Mp: 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27–4.37 (m, 3H), 4.78–4.84 (m, 1H), 5.42–5.47 (m, 1H), 6.91–7.02 (m, 8H), 7.29 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.39–7.47 (m, 1H); anal. Calcd for $C_{23}H_{16}F_5NO_3$: C, 61.47; H, 3.59; N, 3.12; found: C, 61.41; H, 3.65; N, 3.11.

Data for **4w**: yield, 91%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.20–4.24 (m, 1H), 4.76–4.81 (m, 1H), 5.62–5.67 (m, 1H), 6.74 (s, 1H), 6.97–7.04 (m, 5H), 7.18 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.39–7.46 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{23}H_{16}F_5NO_3$ $(M + H)^+$: 450.1123, found: 450.1124.

Data for **4x**: yield, 83%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.14–4.20 (m, 1H), 4.83–4.90 (m, 1H), 5.60–5.66 (m, 1H), 6.281–6.89 (m, 2H), 6.97–7.03 (m, 4H), 7.29–7.36 (m, 4H), 7.40–7.48 (m, 1H); HRMS (ESI) *m/z* calcd for $C_{22}H_{17}F_2NO_2$ $(M + H)^+$: 366.1300, found: 366.1294.

Data for **4y**: yield, 81%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 4.00 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 4.17–4.21 (m, 1H), 4.88–4.93 (m, 1H), 5.64–5.69 (m, 1H), 6.63 (s, 1H), 6.97–7.01 (m, 3H), 7.04 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.42–7.50 (m, 2H), 7.59 (d, $^3J_{HH}$ = 8.6 Hz, 2H); HRMS (ESI) *m/z* calcd for $C_{24}H_{18}F_5NO_3$ $(M + H)^+$: 464.1279, found: 464.1281.

Biological assays

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis. Evaluations are based on a percentage scale of 0–100, in which 0 = no activity and 100 = total kill. The deviations of the tested biological values were <5%.

Acaricidal activity against the eggs of spider mites (*Tetranychus cinnabarinus Boisduval*). The acaricidal activities against the eggs of spider mites of the title compounds **4a–y** and the control compound etoxazole were evaluated by the leaf-dip method.[9,10] Sieva bean plants (*Phaseolus Vulgaris* L.) with primary leaves expanded to 10 cm were selected and cut back to one plant per pot. A small piece was cut from a leaf taken from the main colony and placed on each leaf of the test plants. This was done about 2 h before treatment to allow the mites to move to the test plant and to lay eggs. The size of the piece was varied to obtain about 60–100 mites per leaf. The leaves were kept for no more than 24 h before treatment. The mite-egg-infested leaf was dipped into the test solution for 3 s with agitation and set in the hood to dry, then they were placed in a tube (10 cm inner diameter) lined with a piece of filter paper. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out.

Acaricidal activity against the larvae of spider mites (*Tetranychus cinnabarinus Boisduval*). The acaricidal activities against the larvae of spider mites of the title compounds **4a–y** and the control compound etoxazole were evaluated by the leaf-dip method.[12,13] Mite-egg-infested leaves (choose the eggs which were laid at the same day) were kept at 25 °C for 4 days,

and then they were cut and put on the test leaves as described above. After one day, the larvae were hatched and moved to the fresh leaves. Each leaf had about 60–100 mites. The leaf was cut and dipped into the test solution for 3 s with agitation and set in the hood to dry, then was placed in a tube (10 cm inner diameter) lined with a piece of filter paper. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out.

Larvicidal activity against diamondback moths (*Plutella xylostella linnaeus*). The larvicidal activities of the title compounds **4a–y** and the control compound etoxazole against diamondback moths were tested by the leaf-dip method using the reported procedure.[9–13] Leaf disks (1.8 cm in diameter) were cut from fresh cabbage leaves and then dipped into the test solution for 5 s. After air-drying, the treated leaf disks were placed in a tube (9 × 3 cm inner diameter) lined with a piece of filter paper, and then 10 second-instar diamondback moth larvae were transferred to the tube. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out.

Larvicidal activity against beet armyworms (*Spodoptera exigua*). The larvicidal activities of the title compounds **4a–y** and the control compound etoxazole against beet armyworms were tested by the leaf-dip method using the reported procedure.[11–13] The procedure was the same as the testing method used for the diamondback moths, using 10 second-instar beet armyworms.

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